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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20040511

Application Number: 09/816,467
Filing Date: March 26, 2001
Appellant(s): COEN ET AL.

Timothy B. Donaldson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1 March 2004 (hereinafter, the brief).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. The appellants indicate that the specification of the present application is identical to that of US Application No. 09/501,787 ('787). An Appeal Brief was filed in the '787 application on July 16, 2003 and a Supplemental Appeal Brief was filed January 12, 2004.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The supplemental amendment after final rejection filed on February 3, 2004, has not been entered. Appellants' statement that the amendment filed on February 3, 2004, has not been acted on by the Examiner is incorrect. The amendment filed on February 3, 2004, has been acted on by Examiner on February 27, 2004. The advisory action mailed on February 27, 2004, indicates that the proposed amendment filed February 3, 2004, will be entered for purposes of Appeal and claims 17, 18, 21-23, 34 and 35 remain rejected for the reasons of record.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellants acknowledge that claims 17, 18, 21-23, 34 and 35 stand or fall together in relation to the 35 U.S.C. 103 rejection.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Mueller, G. P. "Toxin-Mediated Transfer and Expression of Genes in Nerve Cells" NTIS Accession No. AD-A290 501/6, Report No. ARO-27890.1-LS (October 12, 1994), p. 1-15.

Hohne-Zell et al., "Functional Characterization of the Catalytic Site of the Tetanus Toxin Light Chain Using Permeabilized Adrenal Chromaffin Cells" FEBS Letters, Vol. 336, No. 1 (December 1993), p. 175-180.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 17, 18, 21-23, 34 and 35 are rejected under 35 U.S.C. U.S.C. 103(a) as being unpatentable over Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) in view of Hohne-Zell et al., 1993 (FEBS Letters, Vol. 336, No. 1, p. 175-180).

Claims 17, 18, 21-23, 34 and 35 are directed to a hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction thereof of at least 11 amino acid residues, a composition containing said hybrid fragment in association with an active molecule, and a hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction

thereof, and further containing a fragment A devoid of its zinc-binding motif located between residues 225 and 245.

Mueller teaches receptor mediated gene transfer in the central nervous system and "tetanus toxin is uniquely specific for uptake into neurons and enters the central nervous system from the circulation with the highest efficiency of any known protein" (e.g. p. 3). Tetanus toxin includes fragment B and fragment C, and contains at least 11 amino acid residues of fragmetn B. Mueller teaches that carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo. The toxic portion of the protein resides in the amino terminal (e.g. p. 3 and 4).

Mueller does not teach a hybrid fragment comprising fragment C of tetanus toxin and at least 11 amino acid residues of fragment B or a hybrid fragment further comprises a fraction of a fragment A devoid of its toxic activity corresponding to zinc-binding motif between amino acid residues 225 and 245.

Hohne-Zell teaches zinc and the putative zinc-binding domain constitute the active site of the tetanus toxin light chain and replacement of histidine (position 233) by cysteine or valine and of glutamate (position 234) by glutamine completely abolished the activity of light chain on calcium induced catecholamine release (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to generate claimed hybrid fragment or composition because Mueller teaches that C-fragment of the tetanus toxin alone is not toxic and the toxic portion of the protein resides in the amino terminal, and in combination with the teaching of Hohne-Zell that the putative zinc-binding domain

constitutes the active site of the tetanus toxin light chain would make it obvious for one of ordinary skill to remove said zinc-binding domain when generating a tetanus toxin fragment for neuron specific transport. It also would have been obvious for one of ordinary skill at the time of the invention to include a portion of fragment B with fragment C of tetanus toxin because the toxic region of tetanus toxin resides in the putative zinc-binding domain, which is at amino terminal, and inclusion of a portion of non-toxic region of tetanus toxin would not contribute to the toxicity of tetanus toxin.

One ordinary skill at the time the invention was made would have been motivated to do so in order to generate a non-toxic tetanus toxin fragment capable of retrograde transport as a carrier molecule for neuron specific gene transfer in vivo as taught by Mueller and Hohne-Zell with reasonable expectation of success.

(11) Response to Argument

Appellants argue that Mueller only teaches the neuronal transport property of the full tetanus toxin, which includes fragment A, B, and C, does not teach or suggest a hybrid tetanus toxin fragment that includes fragment B, or a fraction thereof having at least 11 amino acid residues. Appellants further argue that the term "hybrid fragment" recited in the claims is a necessary element of the claim and the term "fragment" provides a structural element to the claimed invention and cannotes some portion less than the whole (brief, p. 7-11). This is not found persuasive because the instant rejection is an obviousness rejection, and hence Mueller need not teach all claim limitations. It is the combination of references that renders the invention obvious. Mueller teaches receptor-mediated gene transfer in the central nervous system and states that "tetanus toxin is uniquely specific for uptake into neurons and enters the central

nervous system from the circulation with the highest efficiency of any known protein" (e.g. p. 3). Although Mueller does not specifically teach using a " hybrid fragment" of the full tetanus toxin protein as claimed, such as a hybrid tetanus toxin fragment that includes fragment B, or a fraction thereof having at least 11 amino acid residues, Mueller teaches that "tetanus toxin is uniquely specific for uptake into neurons and enters the central nervous system from the circulation with the highest efficiency of any known protein", therefore, Mueller does imply the use of the full tetanus toxin that includes fragments A, B and C. Hohne-Zell teaches that zinc and the putative zinc-binding domain constitute the active site of the tetanus toxin light chain, which is fragment A as disclosed in the specification of the present invention and is part of fragment B as taught by Mueller (see Figure 1). Hohne-Zell also teaches that replacement of histidine (position 233) by cysteine or valine, and of glutamate (position 234) by glutamine completely abolished the inhibition activity of light chain on calcium induced catecholamine release (e.g. abstract), i.e. such mutation abolishes toxic activity of the tetanus toxin. Since the toxic activity of tetanus toxin resides at fragment A, in particular amino acid residues 233 and 234, and Mueller implies the use of the full tetanus toxin that includes fragments A, B and C, it would have been obvious for one of ordinary skill in the art at the time of the invention to use a tetanus toxin devoid of fragment A or devoid of the active site residues at fragment A of the tetanus toxin protein for neuron specific gene transfer in the central nervous system.

Claim 17 reads on a hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction of fragment B having at least 11 amino acid residues and claim 18 reads on a hybrid fragment of tetanus toxin comprising the hybrid fragment of claim 17 and further comprising a fraction of a fragment A devoid of its toxic activity corresponding to the zinc-

binding domain located between residues 225 and 245. Thus, the claimed hybrid fragment of tetanus toxin encompasses a hybrid fragment comprising fragments C and B or a fraction of B of tetanus toxin or a hybrid fragment comprising a full tetanus toxin devoid of the region that contributes to its toxic activity. As discussed above, the toxic activity of tetanus toxin resides at fragment A, in particular amino acid residues 233 and 234, therefore, it would have been obvious for one of ordinary skill in the art at the time of the invention to use a tetanus toxin devoid of fragment A (i.e. comprising only fragments C and B) or devoid of the active site residues at fragment A of the tetanus toxin protein (i.e. comprising fragments C and B and the non-toxic part of fragment A) for gene transfer in the central nervous system. One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate a non-toxic tetanus toxin fragment capable of retrograde transport as a carrier molecule for neuron specific gene transfer in vivo as taught by Mueller and Hohne-Zell with reasonable expectation of success.

Appellants argue that Mueller teaches away from the claimed invention by physically removing fragment B from the tetanus toxin for gene transfer study and teaches that fragment C is sufficient for gene transfer in vivo (brief, p. 11-12). This is not found persuasive because although Mueller suggests that fragment C alone is not toxic and is sufficient for internalization and transport and can be used as carrier molecule for neuron specific gene transfer in vivo (e.g. p. 4, second paragraph), Mueller does not teach that only fragment C should be used for gene transfer in vivo. As discussed above, the toxic activity of tetanus toxin resides at fragment A, in particular amino acid residues 233 and 234, and Mueller teaches that "tetanus toxin is uniquely specific for uptake into neurons and enters the central nervous system from the circulation with

the highest efficiency of any known protein", therefore, Mueller implies the use of the full tetanus toxin that includes fragments A, B and C. Therefore, it would have been obvious for one of ordinary skill in the art at the time of the invention to use a tetanus toxin devoid of fragment A (i.e. comprising only fragments C and B) or devoid of the active site resides at fragment A of the tetanus toxin protein (i.e. comprising fragments C and B and the non-toxic part of fragment A) for neuron specific gene transfer in the central nervous system.

Appellants argue that Hohne-Zell fails to teach or suggest using a tetanus toxin fragment containing fragment C and fragment B (brief, p. 13). This is not found persuasive because although Hohne-Zell alone does not teach using a tetanus toxin containing fragment C and fragment B, the combination of the teachings of Muller and Hohne-Zell would motivate one of ordinary skill in the art to use a tetanus toxin devoid of fragment A (i.e. comprising only fragments C and B) or devoid of the active site resides at fragment A of the tetanus toxin protein (i.e. comprising fragments C and B and the non-toxic part of fragment A) for neuron specific gene transfer in the central nervous system with reasonable expectation of success.

Appellants argue that there is no motivation to combine the teachings of Mueller and Hohne-Zell and Examiner's conclusory statement about generating the claimed hybrid fragments does not provide the clear and particular evidence required to establish the motivation to combine references under 35 U.S.C. 103 (brief, p. 14-15). This is not found persuasive because obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In*

re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Hohne-Zell teaches that the toxic activity of tetanus toxin resides at fragment A, in particular amino acid residues 233 and 234, and Mueller teaches that "tetanus toxin is uniquely specific for uptake into neurons and enters the central nervous system from the circulation with the highest efficiency of any known protein", therefore, Mueller implies the use of the full tetanus toxin that includes fragments A, B and C. Mueller also teaches that the transport activity resides in fragment C. Thus, the teachings of Hohne-Zell and Mueller provide clear and particular evidence that would motivate one of ordinary skill in the art at the time of the invention to use a tetanus toxin devoid of fragment A or devoid of the toxic active site residues at fragment A of the tetanus toxin protein for neuron specific gene transfer in the central nervous system.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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May 17, 2004

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